JAMA | Review

Diagnosis and Management of Resistant Hypertension

A Review

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IMPORTANCE Hypertension, defined as office systolic blood pressure (SBP) 130 mm Hg or greater and/or diastolic blood pressure 80 mm Hg or greater, affects 43.9% of women and 49.5% of men in the US. Approximately 19.7% of patients treated for hypertension have apparent resistant hypertension (blood pressure ≥130/80 mm Hg) despite using 3 or more antihypertensive medications, preferably a renin-angiotensin system blocker, a calcium channel blocker, and a thiazide-type diuretic, at maximally tolerated doses.

OBSERVATIONS Approximately 10% of patients treated for hypertension have true resistant hypertension confirmed with home or 24-hour ambulatory blood pressure monitoring to exclude white-coat hypertension (approximately 37.5% of apparent resistant hypertension) and after excluding medication nonadherence (approximately 50%) and secondary hypertension such as primary aldosteronism (approximately 5%-25%). Conditions associated with resistant hypertension include obesity, diabetes, chronic kidney disease, and sleep apnea. Resistant hypertension is associated with increased risk of cardiovascular death vs controlled blood pressure at 5 years to 10 years (absolute risk increase, 10.3% [95% CI, 8.7%-12.1%]). Lifestyle modifications for resistant hypertension include a low-sodium diet (<1500 mg/d), reducing or avoiding alcohol, 150 min/wk or more of aerobic exercise, and weight loss. Illicit drugs (eg, cocaine) and medications that increase blood pressure (eg, nonsteroid anti-inflammatory drugs, serotonin-norepinephrine reuptake inhibitors) should be avoided. Sleep apnea should be treated when diagnosis is confirmed. Pharmacologic optimization includes use of combination tablets of antihypertensives; intensifying diuretic therapy by using chlorthalidone; and sequential addition of antihypertensive medications using evidence-based algorithms. In a meta-analysis of 20 studies (9 randomized clinical trials [RCTs] and 11 observational studies [331 participants]), use of antihypertensive therapies that combine 2 to 3 medications into a single formulation reduced SBP by −3.99 mm Hg (95% CI, −7.92 to −0.07) vs equivalent doses given separately. For patients with apparent or true resistant hypertension who have an estimated glomerular filtration rate of 45 mL/min/1.73 m^2 or greater and a serum potassium level of 4.5 mmol/L or less, adding spironolactone (25-50 mg/d) compared with placebo lowers office SBP by −13.3 mm Hg (95% CI, −17.89 to −8.72 [4 RCTs]) and 24-hour ambulatory SBP by −8.46 mm Hg (95% CI, −12.54 to −4.38 [2 RCTs]) in a network meta-analysis of 24 RCTs (3485 patients with resistant hypertension). A meta-analysis of 10 RCTs (2478 participants) reported that compared with a sham procedure, catheter-based renal denervation, which disrupts the sympathetic nerves in the renal artery walls, decreased 24-hour ambulatory SBP by −4.4 mm Hg (95% CI, −6.1 to −2.7) and office SBP by −6.6 mm Hg (95% CI, −9.7 to −3.6).

CONCLUSIONS AND RELEVANCE True resistant hypertension affects 10% of patients treated for hypertension and is diagnosed after excluding white-coat hypertension, medication nonadherence, and secondary hypertension such as primary aldosteronism. First-line treatment includes lifestyle modifications, diuretic therapy with chlorthalidone, and combination tablets of antihypertensives. Spironolactone and renal denervation decrease blood pressure in patients with true resistant hypertension.

JAMA. doi:10.1001/jama.2026.1221
Published online March 23, 2026.

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Hypertension, defined as systolic blood pressure (SBP) 140 or greater and/or diastolic blood pressure (DBP) 90 mm Hg or greater or use of medication for hypertension, affects 25% to 30% of adults worldwide.[1] When defined by blood pressure of 130/80 mm Hg or greater or receiving antihypertensive therapy, the 2017-2020 National Health and Nutrition Examination Survey of US adults aged 18 to 80 years reported the prevalence of hypertension as 49.5% (59.0 million) for men and 43.9% (56.3 million) for women.[2] Approximately 19.7% of adults taking antihypertensive medications in the US meet the 2025 American Heart Association/American College of Cardiology (AHA/ACC) diagnosis of apparent resistant hypertension, defined as an office SBP of 130 mm Hg or greater and/or DBP of 80 mm Hg or greater despite use of 3 medications (preferably an angiotensin-converting enzyme [ACE] inhibitor or an angiotensin receptor blocker, a calcium channel blocker, and a thiazide-type diuretic) at maximally tolerated doses.[3] True resistant hypertension is confirmed after exclusion of white-coat hypertension, nonadherence to antihypertensive medications, and secondary causes of hypertension. This review focuses on the epidemiology, pathophysiology, diagnosis, and treatment of apparent and true resistant hypertension (**Box 1**).

Box 1. Common Questions About Resistant Hypertension

How is true resistant hypertension defined and distinguished from apparent resistant hypertension?

Resistant hypertension is defined as systolic blood pressure 130 mm Hg or greater and/or diastolic blood pressure 80 mm Hg or greater despite the use of 3 or more antihypertensive medications of different classes at maximal tolerated doses (preferably including an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, a calcium channel blocker, and a thiazide-type diuretic), after excluding white-coat hypertension, nonadherence to antihypertensive medications, and secondary hypertension (such as primary aldosteronism).

What are the common risk factors or causes of resistant hypertension?

Volume overload due to high sodium intake, primary aldosteronism, inappropriate and renin-independent aldosterone excess without overt primary aldosteronism, obesity, obstructive sleep apnea, and chronic kidney disease are common among patients with resistant hypertension. Nonsteroidal anti-inflammatory drugs, some antidepressants (such as serotonin-norepinephrine reuptake inhibitors), and illicit drugs (such as cocaine) are associated with poor blood pressure control.

How should true resistant hypertension be treated?

Management of true resistant hypertension includes lifestyle modifications (adherence to a low sodium diet [<1500 mg/d], reducing or avoiding alcohol, moderate-intensity exercise [≥150 min/wk of regular, moderate intensity aerobic exercise, and ≥2 d/wk of resistance exercise], and weight loss). For patients with resistant hypertension, the use of combinations pills, intensifying diuretic therapy by using preferably chlorthalidone (especially in patients with chronic kidney disease), and the addition of a mineralocorticoid receptor antagonist (eg, spironolactone) are recommended for patients with estimated glomerular filtration rate of 45 mL/min/1.73 m^2 or greater and serum potassium level of 4.5 mmol/L or less. Patients who experience adverse effects with spironolactone can be switched to amiloride or eplerenone. Other therapeutic options include β-blockers, α_1-adrenergic blockers, centrally acting antihypertensive agents, nondihydropyridine calcium channel blockers, direct vasodilators, or a dual endothelin receptor antagonist (eg, aprocitentan), which may be also used as alternatives to spironolactone in case of adverse events or contraindication or added sequentially to a regimen that includes spironolactone.

Methods

We searched PubMed (MEDLINE) for English-language articles from January 2015 through January 2026 using the terms *resistant hypertension* or *refractory hypertension*. We focused on studies published from 2015 to 2026 to provide evidence aligned with contemporary diagnostic thresholds and guideline definitions but included earlier studies when clinically relevant. We prioritized evidence from randomized clinical trials (RCTs), meta-analyses, and major guideline statements. Reference lists from relevant articles and guidelines were searched for additional pertinent studies. Of 214 manuscripts retrieved from the search, 87 were included in this review, consisting of 25 RCTs, 17 meta-analyses, 5 longitudinal prospective observational studies, 9 cross-sectional studies, 17 guidelines, and 14 pathophysiological reviews.

Epidemiology and Risk Factors

In 2 separate cohort studies (800 and 2316 participants) of patients with hypertension, 19.4% of participants with initially controlled blood pressure with antihypertensive medications progressed to apparent resistant hypertension (blood pressure ≥130/80 mm Hg) over 9 years.[4] In a systematic review and meta-analysis of patients taking antihypertensive medications (91 cross-sectional and cohort studies [3 207 911 participants]), the prevalence of true resistant hypertension at a higher threshold of blood pressure of 140/90 mm Hg or greater was 10.3% (95% CI, 7.6%-13.2%).[5] Higher prevalence of apparent resistant hypertension (up to 50%) and true resistant hypertension (22.9%) is reported among patients with chronic kidney disease (CKD), particularly in those with albuminuria.[5,6]

In a cross-sectional study of 37 061 US patients with apparent resistant hypertension, risk factors associated with resistant hypertension were CKD (odds ratio [OR], 1.84 [95% CI, 1.78-1.90]), Black race (OR, 1.68 [95% CI, 1.62-1.75]), diabetes (OR, 1.58 [95% CI, 1.53-1.63]), obesity (OR, 1.46 [95% CI, 1.42-1.51]), cardiovascular disease (OR, 1.34 [95% CI, 1.30-1.39]), older age (OR, 1.11 [95% CI, 1.10-1.11] for every 5-year increase over age of 17 years), and male sex (OR, 1.06 [95% CI, 1.03-1.10]).[7] A systematic review and meta-analysis (6 observational studies [1465 participants]) reported an association between obstructive sleep apnea (OSA) and resistant hypertension (pooled OR, 2.84 [95% CI, 1.70-3.98]; absolute rates not reported).[8] A meta-analysis of 23 cohort studies with more than 600 000 participants reported an association between daily alcohol consumption and the presence of hypertension with risk ratios of 0.89 (95% CI, 0.84-0.94) for 0 g/d of alcohol, 1.11 (95% CI, 1.07-1.15) for 24 g/d, 1.22 (95% CI, 1.14-1.30) for 36 g/d, and 1.33 (95% CI, 1.18-1.49) for 48 g/d, compared with participants who drank 12 g/d of alcohol.[9,10] Obesity (body mass index ≥30, calculated as weight in kilograms divided by square of height in meters) was present in 29 560 of 60 327 patients (49%) with resistant hypertension in a 2013 US observational study.[7]

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Pathophysiology

The pathophysiology of resistant hypertension involves the complex interplay of several neurohormonal pathways, including inappropriate and renin-independent aldosterone excess[11]; sympathetic,[12] endothelin-1,[13] and vasopressin overactivity[14]; impaired natriuretic peptide system activity[15]; and impaired endothelial function.[16] These factors contribute to volume and sodium overload, increases in arterial stiffness, and kidney fibrosis. Excess dietary sodium intake (≥2300 mg/d) causes low plasma renin activity and promotes volume overload, which diminishes the effectiveness of renin-angiotensin system (RAS) blockers and increases the requirement for diuretics at higher doses or in combination to achieve adequate natriuresis.[17,18] Low dietary potassium intake (<1500 mg/d) may also contribute to elevated blood pressure through mechanisms such as increased sodium retention by the kidneys and increased vascular tone.[19,20] Obstructive sleep apnea may independently increase blood pressure through sympathetic overdrive, renin-angiotensin-aldosterone system activation, endothelial dysfunction, and possible fluid retention.[21,22]

Clinical Presentation

Office Blood Pressure Measurements

Patients with apparent resistant hypertension take 3 or more antihypertensive medications and have elevated blood pressure (≥130/80 mm Hg), typically detected in the office.[3,23,24] While the 2025 AHA/ACC guidelines use a threshold of office SBP of 130 mm Hg or greater and/or of DBP 80 mm Hg or greater to define resistant hypertension,[3] the 2023 European Society of Hypertension and the 2024 European Society of Cardiology guidelines define resistant hypertension with an office blood pressure of 140/90 mm Hg or greater.[23,24] Office blood pressure measurements should be obtained with the patient in the seated position for at least 5 minutes using a proper technique with a validated oscillometric electronic device and a correct cuff size[3,23,24] and recorded as the average of at least 2 measurements taken at least 1 minute apart. Patients with apparent resistant hypertension based on office blood pressure should undergo out-of-office blood pressure measurement with either home blood pressure monitoring or 24-hour ambulatory blood pressure monitoring (ABPM) to exclude white-coat effect.[3]

Out-of-Office Blood Pressure Measurements

Resistant hypertension with home blood pressure monitoring is defined as an average of 130/80 mm Hg or greater for all recorded blood pressures, which corresponds to the office blood pressure threshold of 130/80 mm Hg or greater.[3,23,24] Self-monitoring of blood pressure at home requires that patients use a validated automated device with a correct cuff size matched to the arm size and receive instructions from a clinician or a trained nurse. Measurements should be taken twice daily for a minimum of 3 days, but preferably over 1 week, prior to antihypertensive medication intake.[3,23] The patient should be in the seated position for 5 minutes of rest and then should record 2 blood pressure measurements taken 1 minute apart.

Out-of-office measures can also be obtained with ABPM, which is performed with a small fully automated portable blood pressure monitor worn on the upper arm for 24 hours. Over the 24-hour cycle, ABPM provides blood pressure measurements every 15 to 30 minutes during daytime and at less frequent intervals during nighttime (30-60 minutes). The 24-hour ambulatory blood pressure threshold for resistant hypertension is an average of 125/75 mm Hg or greater in the US guidelines and 130/80 mm Hg or greater in the European guidelines.[23,24]

Differentiating Apparent and True Resistant Hypertension

The differential diagnosis for apparent resistant hypertension includes white-coat hypertension, defined as office blood pressure 130/80 mm Hg or greater, with home blood pressure less than 130/80 mm Hg or 24-hour ABPM less than 125/75 mm Hg, and medication nonadherence (**Figure**).[3,23,24] In an observational cohort study from Spain, 3110 of 8295 patients (37.5%) with apparent resistant hypertension (office blood pressure ≥140/90 mm Hg) had 24-hour ambulatory blood pressure less than 130/80 mm Hg.[25] In other studies, nonadherence has been reported in up to 50% of patients.[26] Assessment of adherence should include a nonjudgmental discussion with patients and review of pharmacy refill data. In some cases, if uncertainty persists, direct measurement of antihypertensive drug or metabolite levels in urine or blood can be performed, typically using liquid chromatography–tandem mass spectrometry.[26]

Secondary Hypertension

Secondary hypertension is the presence of hypertension attributable to identifiable and often treatable underlying conditions (**Table 1**).[3,23,24] The prevalence of secondary hypertension is higher among patients with resistant hypertension (≈25%) than among hypertensive individuals without resistant hypertension (≈10%) (Table 1).[3,27,28] All patients with resistant hypertension should be screened for secondary causes of hypertension, particularly primary aldosteronism, which is characterized by high plasma aldosterone levels and low plasma renin levels when measured simultaneously, leading to an elevated aldosterone-to-renin ratio.[3,23,24] Primary aldosteronism is the most common secondary cause of resistant hypertension (range, 5%-25%).[3,23,24,27-29]

Medication Review

Patients with apparent resistant hypertension should also have a medication review to identify medications that may increase blood pressure directly or counteract the blood pressure–lowering effect of antihypertensive treatments (**Box 2**).[30] In a US cross-sectional survey (National Health and Nutrition Examination Survey) including 27 599 individuals, 18.5% of adults 18 years or older with hypertension reported using medications that may increase blood pressure, including antidepressants (8.7%), nonsteroidal anti-inflammatory drugs (6.5%), steroids (1.9%), and oral estrogens (1.7%).[31] Whenever feasible, all medications that may increase blood pressure should be discontinued or replaced with alternatives that do not affect blood pressure, because even modest drug-induced blood pressure elevations (2-5 mm Hg) may increase cardiovascular risk in patients with resistant hypertension. However, decisions about medication withdrawal should be individualized based on the indication and clinical benefit of the drug, which may outweigh a modest increase in blood pressure, the availability of alternative medications, and patient preferences.

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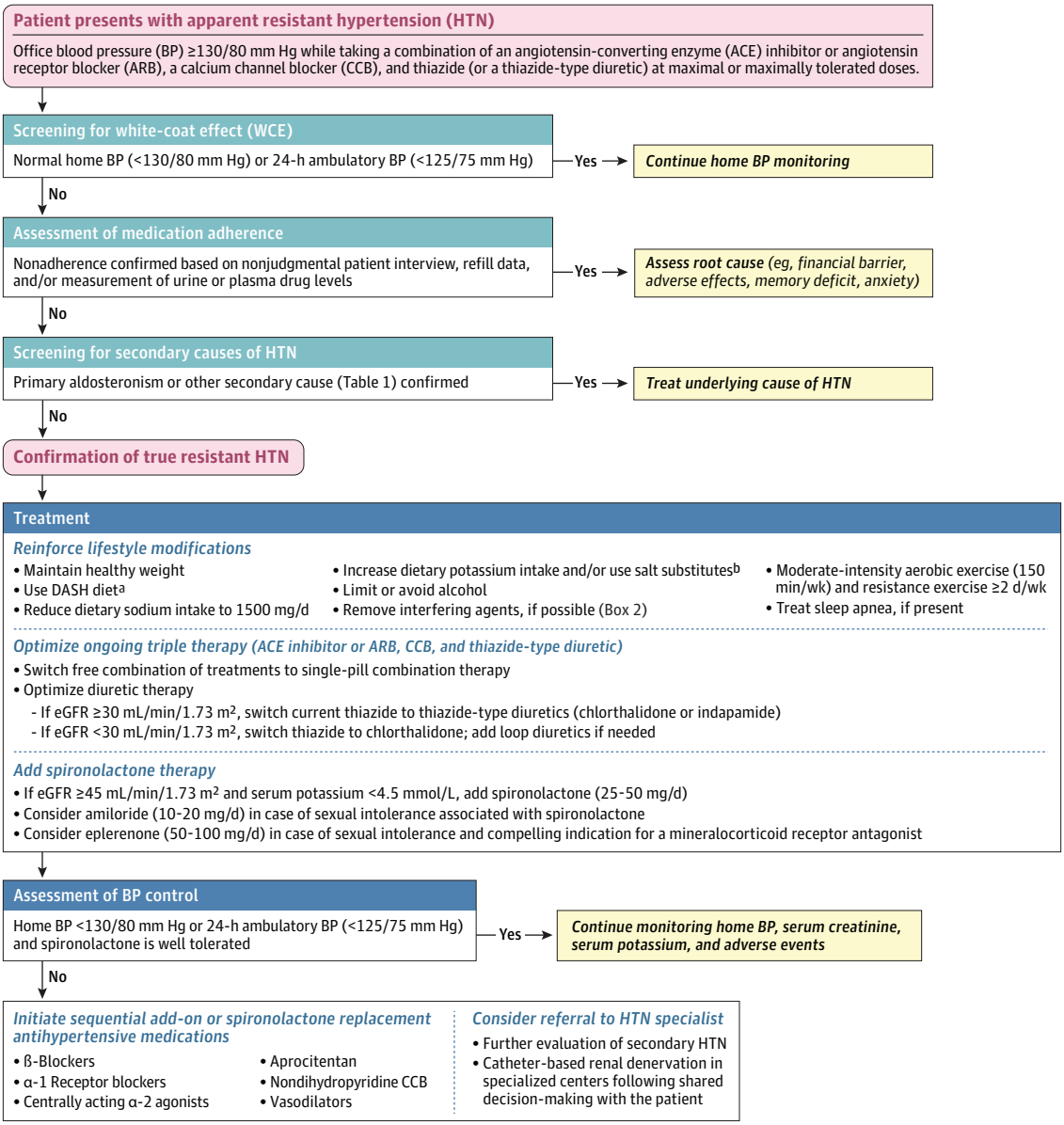
Figure. Algorithm for Management of Resistant Hypertension


Patient presents with apparent resistant hypertension (HTN)
Office blood pressure (BP) ≥130/80 mm Hg while taking a combination of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), a calcium channel blocker (CCB), and thiazide (or a thiazide-type diuretic) at maximal or maximally tolerated doses.
Screening for white-coat effect (WCE)
Normal home BP (<130/80 mm Hg) or 24-h ambulatory BP (<125/75 mm Hg)
Yes
Continue home BP monitoring
No
Assessment of medication adherence
Nonadherence confirmed based on nonjudgmental patient interview, refill data, and/or measurement of urine or plasma drug levels
Yes
Assess root cause (eg, financial barrier, adverse effects, memory deficit, anxiety)
No
Screening for secondary causes of HTN
Primary aldosteronism or other secondary cause (Table 1) confirmed
Yes
Treat underlying cause of HTN
No
Confirmation of true resistant HTN
Treatment
Reinforce lifestyle modifications
• Maintain healthy weight
• Use DASH diet[a]
• Reduce dietary sodium intake to 1500 mg/d
• Increase dietary potassium intake and/or use salt substitutes[b]
• Limit or avoid alcohol
• Remove interfering agents, if possible (Box 2)
• Moderate-intensity aerobic exercise (150 min/wk) and resistance exercise ≥2 d/wk
• Treat sleep apnea, if present
Optimize ongoing triple therapy (ACE inhibitor or ARB, CCB, and thiazide-type diuretic)
• Switch free combination of treatments to single-pill combination therapy
• Optimize diuretic therapy
- If eGFR ≥30 mL/min/1.73 m², switch current thiazide to thiazide-type diuretics (chlorthalidone or indapamide)
- If eGFR <30 mL/min/1.73 m², switch thiazide to chlorthalidone; add loop diuretics if needed
Add spironolactone therapy
• If eGFR ≥45 mL/min/1.73 m² and serum potassium <4.5 mmol/L, add spironolactone (25-50 mg/d)
• Consider amiloride (10-20 mg/d) in case of sexual intolerance associated with spironolactone
• Consider eplerenone (50-100 mg/d) in case of sexual intolerance and compelling indication for a mineralocorticoid receptor antagonist
Assessment of BP control
Home BP <130/80 mm Hg or 24-h ambulatory BP (<125/75 mm Hg) and spironolactone is well tolerated
Yes
Continue monitoring home BP, serum creatinine, serum potassium, and adverse events
No
Initiate sequential add-on or spironolactone replacement antihypertensive medications
• ß-Blockers
• α-1 Receptor blockers
• Centrally acting α-2 agonists
• Aprocitentan
• Nondihydropyridine CCB
• Vasodilators
Consider referral to HTN specialist
• Further evaluation of secondary HTN
• Catheter-based renal denervation in specialized centers following shared decision-making with the patient

[a]DASH indicates Dietary Approaches to Stop Hypertension (https://www.nhlbi.nih.gov/education/dash-eating-plan).

[b]Except in patients with estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2.

Management of True Resistant Hypertension

Management of true resistant hypertension involves intensifying lifestyle modifications, and stepwise addition of antihypertensive medications targeting different pathophysiological mechanisms (Figure). Using evidence-based treatment algorithms,[3,23,24,27] treatment should be individualized, based on patient preferences, comorbid conditions, kidney function, potential medication adverse effects, and drug interactions. Treatment focuses on mean blood pressure reduction as the primary target, because absolute blood pressure lowering is an accepted surrogate marker to reduce cardiovascular morbidity and mortality.[32-34] For example, a meta-analysis of 48 randomized trials (344 716 participants; median follow-up, 4.15 years) reported that a 5-mm Hg decrease in office SBP was associated with decreased incidence of major adverse cardiovascular events among participants with both prior cardiovascular disease (absolute risk reduction, −1.6% [95% CI, −1.9% to −1.2%]; hazard ratio [HR], 0.89 [95% CI, 0.86-0.92]) and without prior cardiovascular disease (absolute risk reduction, −2.2% [95% CI, −2.5% to −1.9%]; HR, 0.91 [95% CI, 0.89-0.94]).[32,33]

Lifestyle Modifications

Patients with resistant hypertension can decrease blood pressure by reducing sodium and alcohol intake, increasing dietary potassium intake, or using salt substitutes (except in those with estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m^2), using the Dietary Approaches to Stop Hypertension eating plan and en-

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Table 1. Common and Uncommon Causes of Secondary Hypertension[a]

Secondary causes of hypertension	Prevalence, %	Indications for screening
Common causes		
Obstructive sleep apnea	25-50	Snoring, gasping during sleep; daytime sleepiness; resistant hypertension
Chronic kidney disease	14	Diabetes, obstruction, hematuria; urinary frequency and nocturia; urinary incontinence, analgesic abuse; family history of polycystic kidney disease; elevated serum creatinine level; abnormal urinalysis
Primary aldosteronism	5-25	Resistant hypertension; hypertension with hypokalemia (spontaneous or diuretic induced); hypertension and muscle cramps or weakness; hypertension and incidentally discovered adrenal mass; hypertension and obstructive sleep apnea; hypertension and family history of early-onset hypertension or stroke
Drug- or alcohol-induced	2-20	See Box 2 for details
Renovascular hypertension	0.1-5	Resistant hypertension; hypertension with abrupt onset or worsening or increasingly difficult to control; generalized atherosclerotic disease (coronary or peripheral artery disease; carotid, abdominal, or femoral bruit; abdominal systolic diastolic bruit; flash pulmonary edema [atherosclerotic renal artery stenosis]); acute deterioration of renal function (eGFR decrease of 30% or greater) after RAS blocker initiation, recent renal insufficiency, small unilateral kidney; abdominal or lumbar bruit; early-onset hypertension, especially in women (renal artery stenosis due to fibromuscular dysplasia)
Uncommon causes		
Hypothyroidism	<1	Dry skin; cold intolerance; constipation; hoarseness; weight gain
Hyperthyroidism	<1	Warm, moist skin; heat intolerance; nervousness; tremulousness; palpitations, insomnia; weight loss; eye signs (upper eyelid retraction, Graves orbitopathy); diarrhea; proximal muscle weakness; goiter, thyroid nodule
Pheochromocytoma/paraganglioma	<0.6	Resistant hypertension; paroxysmal hypertension or crisis superimposed on sustained hypertension; blood pressure lability, headache, sweating, palpitations, piloerection; positive family history of pheochromocytoma/paraganglioma or presence of associated genetic diseases (multiple endocrine neoplasia type 2 syndrome, von Hippel-Lindau, type 1 neurofibromatosis); adrenal incidentaloma
Aortic coarctation (undiagnosed or repaired)	0.1	Young adult with hypertension (age <30 y), diminished femoral pulses; blood pressure higher in upper extremities than in lower extremities; absent femoral pulses; continuous murmur over patient's back or chest or abdominal bruit; left thoracotomy scar (postoperative)
Cushing syndrome	<0.1	Rapid weight gain with central distribution; proximal muscle weakness; easy bruising; facial plethora; depression; hyperglycemia

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system.

[a] Adapted from the 2025 American Heart Association guidelines.[3]

gaging in regular exercise.[3,19] The AHA recommends sodium intake of less than 1500 mg/d for most adults with hypertension.[3] In a meta-analysis (21 RCTs [31 949 participants]), use of salt substitutes that replace approximately 25% of sodium chloride with potassium chloride, compared with regular salt, was associated with lower SBP (−4.61 mm Hg [95% CI, −6.07 to −3.14]) and lower DBP (−1.61 mm Hg [95% CI, −2.42 to −0.79]).[35]

A meta-analysis of 25 RCTs with 4874 participants reported that SBP decreased by −1.05 mm Hg (95% CI, −1.43 to −0.66) per kilogram of weight loss.[36] An RCT (140 patients with resistant hypertension) reported that a 4-month center-based program that included dietary counseling, weight management, and exercise reduced 24-hour ambulatory SBP at the end of the intervention by −7.0 mm Hg (95% CI, −8.5 to −4.0), compared with no change after a single counseling session (−0.3 mm Hg [95% CI, −4.0 to 3.4]).[37] Similarly, a 12-week aerobic exercise training program composed of 3 supervised training sessions per week including a 10-minute warm-up, 40 minutes of aerobic exercise (cycling and/or walking at 50% to 70% of maximum oxygen consumption and a 10-minute cooldown) resulted in reductions in 24-hour ambulatory SBP by −7.1 mm Hg (95% CI, −12.8 to −1.4) compared with usual care in a single-blinded RCT in patients with resistant hypertension.[38] The 2025 AHA guideline recommends 150 minutes or more per week of regular, moderate-intensity aerobic exercise and 2 or more days per week of resistance exercise for all patients with hypertension.[3]

In a meta-analysis of 36 RCTs with 2865 participants, among individuals consuming 2 or fewer alcoholic drinks per day, reductions in alcohol intake were not associated with significant blood pressure changes. In contrast, among those consuming more than 2 drinks per day, reduced alcohol intake was associated with greater blood pressure reductions. The greatest reductions were observed among participants consuming 6 or more drinks per day who reduced intake by approximately 50%, with mean decreases in SBP of −5.50 mm Hg (95% CI, −6.70 to −4.30) and DBP of −3.97 mm Hg (95% CI, −4.70 to −3.25).[39]

The 2025 ACC/AHA guidelines[3] recommend screening patients with resistant hypertension for OSA with validated instruments such as the STOP-Bang Questionnaire.[40] For patients with resistant hypertension and OSA, continuous positive airway pressure therapy reduced 24-hour ambulatory SBP by an average of −5.92 mm Hg (95% CI, −8.72 to −3.11) vs control in a meta-analysis of 12 RCTs and 718 participants.[41]

Pharmacologic Therapy

The preferred medication combinations to treat apparent resistant hypertension are an ACE inhibitor or an angiotensin receptor blocker; a calcium channel blocker (typically a long-acting dihydropyridine); and a thiazide-type diuretic, preferably using single-pill combination formulations when possible (**Table 2**).[3,23,24,27] A systematic review and meta-analysis (9 RCTs and 11 observational studies [331 participants]) reported that single-pill formulations that combined 2 to 3 medications decreased SBP by −3.99 mm Hg (95% CI, −7.92 to −0.07) compared with equivalent doses given as separate formulations.[42]

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Box 2. Medications and Substances Increasing Blood Pressure

Drugs or Substances Associated With Apparent Mineralocorticoid Excess or Renin-Angiotensin System Activation
- Glucocorticoids and their derivatives
- Glycyrrhizin (licorice)
- Ketoconazole, itraconazole
- Abiraterone acetate
- Synthetic estrogens combined with progestin

Drugs or Substances With Direct Vasopressor Properties
- Immunosuppressive agents (cyclosporine, tacrolimus, and calcineurin inhibitors)
- Recombinant human erythropoietin
- Drugs targeting the vascular endothelial growth factor pathway, including monoclonal antibodies and small-molecule receptor tyrosine kinase inhibitors
- Poly (ADP-ribose) polymerase inhibitors (ovarian cancer)

Drugs or Substances Activating the Sympathetic Nervous System
- Illicit drugs of abuse, such as cocaine and amphetamines
- Epinephrine or phenylephrine derivatives present in over-the-counter oral, nasal, or ophthalmic decongestants
- Ephedrine alkaloids (ephedra or herbal ma-huang)
- Antidepressants, such as serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic agents such as amitriptyline
- Appetite suppressants for weight loss (but not incretin drugs)
- Modafinil, a nonamphetamine stimulant

Drugs or Substances With Diverse Mechanisms of Action
- Antiretroviral drugs (lopinavir and ritonavir)
- Nonselective nonsteroidal anti-inflammatory drugs, acetaminophen and selective cyclooxygenase 2 inhibitors
- Bruton tyrosine kinase inhibitors (for chronic lymphocytic leukemia, various lymphomas, etc)
- Teriflunomide (pyrimidine synthesis inhibitor for multiple sclerosis)
- Alcohol

Diuretics

For patients with resistant hypertension and eGFR of 30 mL/min/1.73 m^2 or greater, 2025 ACC/AHA guidelines recommend switching hydrochlorothiazide to longer-acting thiazide-type diuretics such as chlorthalidone (12.5-25 mg/d) or indapamide (1.25-2.5 mg/d as immediate-release formulation or 1.5 mg/d as slow-release formulation, although slow-release indapamide is not available in the US).[3,23,24,27] A meta-analysis of 14 RCTs that included 883 patients with office SBP of 140 mm Hg or greater reported that compared with hydrochlorothiazide, SBP was lowered more for both indapamide (mean difference, −5.1 mm Hg [95% CI, −8.7 to −1.6]) and chlorthalidone (mean difference, −3.6 mm Hg [95% CI, −7.3 to 0.0]).[43] However, in an RCT (13 523 participants with hypertension, aged ≥65 y and treated with hydrochlorothiazide) reported no significant difference in major cardiovascular outcomes between those randomized to switch to chlorthalidone (12.5 or 25 mg daily) or to continue hydrochlorothiazide (25 or 50 mg daily), over a median follow-up of 2.4 years.[44]

For patients with resistant hypertension and CKD stage 4 or higher, the 2025 AHA/ACC guideline supports using either chlorthalidone with addition of a loop diuretic if further volume control is required or a loop diuretic alone.[3] In an RCT of 160 patients with CKD stage 4 and 24-hour ambulatory blood pressure between 130/80 mm Hg and less than 160/100 mm Hg while receiving at least 1 antihypertensive drug (60% were receiving a loop diuretic), the addition of chlorthalidone (mean dose, 23.1 mg/d) lowered 24-hour ambulatory SBP after 12 weeks of therapy by −11.0 mm Hg (95% CI, −13.9 to −8.1) compared with the placebo response of −0.5 mm Hg (95% CI, −3.5 to 2.5).[45]

The 2025 AHA/ACC guideline recommends rechecking kidney function and serum electrolyte levels 2 to 4 weeks after increasing diuretic doses, switching to loop diuretics or combining thiazide-type diuretics and loop diuretics, or initiating or changing doses of mineralocorticoid receptor antagonists (MRAs).[3,23,24,27] Hypokalemia from intensified diuretic therapy can be corrected by adding potassium-sparing diuretics (eg, amiloride or triamterene) or MRAs which will further decrease blood pressure (see below).[46] Potassium supplements can also correct hypokalemia but are less effective at standard doses than potassium-sparing diuretics.[47,48] An initial and rapid decrease in eGFR over 15 to 30 days in the setting of improved blood pressure control can occur, particularly in individuals taking RAS blockers.[49,50] A decline in eGFR of less than 30% within 30 days of initiation or escalation of antihypertensive therapy, which occurs due to decreased kidney perfusion pressure associated with improved blood pressure control, does not indicate structural kidney injury[51] and does not require dose reduction or discontinuation of antihypertensive therapy.[49,52] In contrast, a decline in eGFR of 30% or greater within 30 days of antihypertensive initiation, especially in patients receiving RAS blockers, may suggest the presence of renal artery stenosis.[53]

Mineralocorticoid Receptor Antagonists

For patients with true resistant hypertension, the addition of MRAs is recommended in the absence of contraindications such as an eGFR less than 30 mL/min/1.73 m^2 (per European guidelines)[23] or less than 45 mL/min/1.73 m^2 (per US guidelines)[3] or serum potassium concentration greater than 4.5 mmol/L (**Table 3**).[3,23,24,27]

Spironolactone

A network meta-analysis of 24 RCTs that included 3485 patients with resistant hypertension and compared treatment options for management of resistant hypertension reported that compared with placebo, spironolactone decreased office SBP by −13.3 mm Hg (95% CI, −17.89 to −8.72 [4 RCTs]) and 24-hour ambulatory SBP by −8.46 mm Hg (95% CI, −12.54 to −4.38 [2 RCTs]).[54] Another meta-analysis of 12 RCTs that included 1655 patients with resistant hypertension reported that compared with placebo, spironolactone increased serum potassium levels by 0.20 mmol/L (95% CI, 0.05-0.35).[61] The risk of hyperkalemia with MRA therapies is higher among those 65 years or older with higher dietary potassium intake, elevated baseline serum potassium level, higher MRA dose, comorbidities such as CKD, diabetes, heart failure, and use of medications such as RAS blockers, nonsteroidal anti-inflammatory drugs, heparin, trimethoprim-sulfamethoxazole, and β-blockers.[62] Potassium binders including patiromer[63] or sodium zirconium cyclosilicate[64] can decrease the risk of hyperkalemia with MRAs. In the AMBER trial, among 295 patients with resistant hypertension taking spironolactone who had an eGFR of 25 to 45 mL/min/1.73 m^2 and baseline serum potassium level less than 5.1 mmol/L, the incidence of hyperkalemia (≥5.5 mmol/L) meeting protocol-specified

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Table 2. Commonly Used Antihypertensive Medications in Fixed-Dose Combination Available in the US[a]

Antihypertensive class	Medication combination	Dose range
ACE inhibitor in dual combination		
With thiazide-type diuretic	Benazepril + hydrochlorothiazide	10 mg/12.5 mg to 20 mg/25 mg
	Captopril + hydrochlorothiazide	25 mg/15 mg to 50 mg/25 mg
	Enalapril + hydrochlorothiazide	5 mg/12.5 mg to 10 mg/25 mg
	Fosinopril + hydrochlorothiazide	10 mg/12.5 mg to 20 mg/12.5 mg
	Lisinopril + hydrochlorothiazide	10 mg/12.5 mg to 20 mg/25 mg
	Moexipril + hydrochlorothiazide	7.5 mg/12.5 mg to 15 mg/25 mg
	Quinapril + hydrochlorothiazide	10 mg/12.5 mg to 20 mg/25 mg
With calcium channel blocker	Benazepril + amlodipine	10 mg/2.5 mg to 40 mg/10 mg
	Perindopril + amlodipine	3.5 mg/2.5 mg to 14 mg/10 mg
	Trandolapril + verapamil	1 mg/240 mg to 4 mg/240 mg
Angiotensin receptor blocker in dual combination		
With thiazide-type diuretic	Azilsartan + chlorthalidone	40 mg/12.5 mg to 40 mg/25 mg
	Candesartan + hydrochlorothiazide	16 mg/12.5 mg to 32 mg/25 mg
	Irbesartan + hydrochlorothiazide	150 mg/12.5 mg to 300 mg/25 mg
	Losartan + hydrochlorothiazide	50 mg/12.5 mg to 100 mg/25 mg
	Olmesartan + hydrochlorothiazide	20 mg/12.5 mg to 40 mg/25 mg
	Telmisartan + hydrochlorothiazide	40 mg/12.5 mg to 80 mg/25 mg
	Valsartan + hydrochlorothiazide	80 mg/12.5 mg to 320 mg/25 mg
With calcium channel blocker	Olmesartan + amlodipine	20 mg/5 mg to 40 mg/10 mg
	Telmisartan + amlodipine	40 mg/5 mg to 80 mg/10 mg
	Valsartan + amlodipine	160 mg/5 mg/12.5 mg to 320 mg/10 mg/25 mg
With β-blocker	Valsartan + nebivolol	80 mg/5 mg
Angiotensin receptor blocker in triple combination		
With calcium channel blocker + thiazide-type diuretic	Olmesartan + amlodipine + hydrochlorothiazide	20 mg/5 mg/12.5 mg to 40 mg/10 mg/25 mg
	Valsartan + amlodipine + hydrochlorothiazide	160 mg/5 mg/12.5 mg to 320 mg/10 mg/25 mg
	Telmisartan + amlodipine + indapamide	10/1.25/0.625 mg; 20/2.5/1.25 mg; and 40/5/2.5 mg
β-Blocker in dual combination		
With thiazide-type diuretic	Atenolol + chlorthalidone	50 mg/25 mg to 100 mg/25 mg
	Bisoprolol + hydrochlorothiazide	2.5 mg/6.25 mg to 10 mg/6.25 mg
	Metoprolol tartrate + hydrochlorothiazide	50 mg/25 mg to 100 mg/50 mg
Thiazide-type diuretics in dual combination		
With potassium-sparing diuretic	Hydrochlorothiazide + amiloride	50 mg/5 mg
	Hydrochlorothiazide + triamterene	25 mg/37.5 mg to 50 mg/75 mg
With mineralocorticoid receptor antagonist	Hydrochlorothiazide + spironolactone	25 mg/25 mg

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

[a] Adapted from the 2025 American Heart Association/American College of Cardiology guidelines[3]; see also https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed September 3, 2025) for more information.

withdrawal of spironolactone over 12 months was lower among those receiving patiromer (7%) vs placebo (23%).[63]

Spironolactone may cause dose-related antiandrogenic and progestogenic adverse effects such as menstrual irregularities in women (18% taking 50-100 mg daily dose)[65] and breast tenderness or gynecomastia in men (17%).[65,66] In the Randomized Aldactone Evaluation Study (RALES), 9.1% of men (603 participants) treated with 25 mg/d spironolactone for heart failure developed gynecomastia, compared with 1.3% in the placebo group (614 participants, $P < .001$ for the comparison).[67] Among 5485 participants in the Hypertension Detection and Follow-Up Program (HDFP), Stepped Care, 1.6% of hypertensive men discontinued spironolactone due to impotence compared with 4.4% discontinuing chlorthalidone due to impotence over a 5-year follow-up period.[68] However, spironolactone-induced impotence is likely underreported, given that erectile dysfunction affects approximately 15% to 20% of the general male population and is nearly twice as prevalent among hypertensive individuals.[69]

Eplerenone

The steroidal MRA eplerenone, which is associated with rates of hyperkalemia similar to those for spironolactone, is more selective for the mineralocorticoid receptor than spironolactone. Because eplerenone has no effect on androgen and progesterone receptors, it is an alternative treatment to spironolactone, especially for male patients with resistant hypertension, with gynecomastia occurring in only 0.5%.[66] However, eplerenone is short-acting and less potent than spironolactone and is typically dosed at 50 mg daily to 50 mg

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Table 3. Antihypertensive Medications for True Resistant Hypertension (Patient Receiving ≥3 Antihypertensive Medications)[a]

Medication (daily dose)	Mechanism of action	Efficacy (treatment vs control)	Adverse effects
Preferred medications[b]			
Spironolactone (25-50 mg)	Mineralocorticoid receptor antagonism	Network meta-analysis in resistant hypertension[54] Mean difference in office SBP vs placebo: −13.30 mm Hg (95% CI, −17.89 to −8.72) Mean difference in 24-h ambulatory SBP vs placebo: −8.46 mm Hg (95% CI, −12.54 to −4.38)	Hyperkalemia (≈3%-5%), acute kidney injury (relative risk, ≈2), sexual impotence (≈9%), gynecomastia (relative risk, ≈5), and menstrual irregularities compared with placebo or standard care
Eplerenone (50-100 mg) (in case of antiandrogenic or progestogenic adverse effects of spironolactone)	Mineralocorticoid receptor antagonism	Cochrane database[55] Eplerenone has only been evaluated in patients with uncontrolled hypertension Mean difference in office SBP vs placebo: −9.21 mm Hg (95% CI, −11.08 to −7.34) Comparative trial in primary hypertension[56] Eplerenone is less potent than spironolactone: mean changes in office SBP for eplerenone (50 mg and 100 mg) twice a day are approximately 50% to 75% of those observed with spironolactone (50 mg) twice a day	Risk of hyperkalemia and acute kidney injury compared with placebo or standard care No antiandrogenic or progestogenic effects
Alternative treatments[c]			
Amiloride (10-20 mg)[d]	Epithelial sodium channel blocker	Amiloride noninferior to spironolactone in patients with resistant hypertension[57,58]	Hyperkalemia
β-Blockers (eg, bisoprolol [5-10 mg])	Selective β1-receptor blockade	Network meta-analysis in resistant hypertension[54] Mean difference in office SBP vs placebo: −8.44 mm Hg (95% CI, −15.48 to −1.40) Mean difference in 24-h ambulatory SBP vs placebo: −7.10 mm Hg (95% CI, −18.12 to 3.92)	Fatigue, bradycardia, sexual impotence
α-1 Blockers (eg, doxazosin [4-8 mg])	α1-adrenergic blockade	Network meta-analysis in resistant hypertension[54] Mean difference in office SBP vs placebo: −7.62 mm Hg (95% CI, −15.86 to 0.62)	Orthostatic hypotension, falls and fractures
Centrally acting sympatholytic medications (eg, clonidine [0.1-0.3 mg] twice daily)	Central α-2 receptor agonist	ReHOT study[59] Office blood pressure decreases from baseline to 3 mo: Clonidine: −13.7 mm Hg (95% CI, −18.4 to −9.0) vs spironolactone: −15.1 mm Hg (95% CI, −19.7 to 10.6) Network meta-analysis in resistant hypertension[54] Mean difference in office SBP vs placebo: −11.90 mm Hg (95% CI, −23.29 to −0.52) Mean difference in 24-h ambulatory SBP vs placebo: −4.26 mm Hg (95% CI, −12.10 to 3.59)	Somnolence, dry mouth, constipation, orthostatic hypotension, impotence, rebound hypertension[60]
Aprocitentan (12.5 mg)	Dual endothelin receptor antagonist	PRECISION trial[13] Mean difference in unattended office SBP vs placebo: −3.8 mm Hg (97.5% CI, −6.8 to −0.8) Mean difference in 24 h ambulatory SBP: −4.2 mm Hg (95% CI, −6.2 to −2.1)	Edema or fluid retention (9%)

Abbreviations: eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure.

[a] Preferred medications are an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, calcium channel blocker, and thiazide-type diuretic.

[b] For patient with true resistant hypertension (if eGFR ≥45 mL/min/1.73 m^2 and serum potassium <4.5 mmol/L).

[c] When mineralocorticoid receptor antagonists are contraindicated or not tolerated, followed by subsequent lines of treatment sequentially added.

[d] If eGFR is 45 mL/min/1.73 m^2 or greater and serum potassium level is less than 4.5 mmol/L. Should not be given with an MRA.

twice daily to achieve antihypertensive effects (mean difference in office SBP, −9.21 mm Hg [95% CI, −11.08 to −7.34 mm Hg] compared with placebo) (Table 3).[55,56,70] Eplerenone is not approved for hypertension treatment in many European countries.[66]

Other Antihypertensive Medications for Treatment of Resistant Hypertension

For patients who experience adverse effects with MRA, amiloride (10-20 mg daily) may be considered[57] if eGFR is 45 mL/min/1.73 m^2

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or greater and serum potassium level is 4.5 mmol/L or less. A prospective, open-label RCT in South Korea (118 patients with resistant hypertension) reported that low-dose amiloride (5-10 mg/d) was noninferior to low-dose spironolactone (12.5-25 mg/d) in lowering home SBP at week 12, with a between-group difference in home SBP of −0.68 mm Hg (90% CI, −3.50 to 2.14) and home SBP control rates (<130 mm Hg) of 66.1% and 55.2%, respectively (P = .23).[58] Other therapeutic options include β-blockers,[54,71] α-1 blockers,[54,71] centrally acting antihypertensive medications,[54,59,60] nondihydropyridine calcium channel blockers, or direct vasodilators, which may be also used as alternatives to spironolactone or added sequentially to a regimen that includes spironolactone. A dual endothelin receptor antagonist (eg, aprocitentan [12.5 mg/d]) may also be used for patients with resistant hypertension who are intolerant of MRAs or for whom MRAs are contraindicated, although studies have not directly compared aprocitentan with MRAs or other medications for true resistant hypertension (Table 3).[3]

Direct vasodilators such as hydralazine or minoxidil may cause severe fluid retention requiring increased doses of loop diuretics and reflex sympathetic tachycardia that may need treatment with β-blockers.[23,27] Aprocitentan may cause peripheral edema, fluid retention, and worsening heart failure, particularly in patients with CKD or prior heart failure (Table 3).[13,72] Aprocitentan is contraindicated during pregnancy. The high cost of aprocitentan may also limit access.

Renal Denervation

Renal denervation is a minimally invasive catheter-based procedure to treat resistant hypertension despite optimal pharmacologic therapy in patients with eGFR of 40 mL/min/1.73 m^2 or greater and suitable renal artery anatomy (renal artery diameter of 3-8 mm, length ≥20 mm, and no significant renal artery stenosis).[3,23,24,73,74] The procedure uses a thin dedicated catheter introduced via the femoral artery that is subsequently inserted into the renal arteries to delivery radiofrequency or ultrasound energy to disrupt the sympathetic nerves located within the adventitial layer of the renal artery, thus attenuating both afferent and efferent renal sympathetic nerve activity.[73,74] This treatment reduces systemic blood pressure through suppression of renin secretion, promotion of natriuresis, and diminution of central sympathetic outflow.[73,74]

Sham-controlled trials[75-78] and a meta-analysis of 10 RCTs (2478 patients; 9 studies required blood pressure of 140/90 mm Hg or greater and 4 explicitly required resistant hypertension)[79] have demonstrated that renal denervation compared with a sham procedure reduced 24-hour ambulatory SBP by −4.4 mm Hg (95% CI, −6.1 to −2.7) and office SBP by −6.6 mm Hg (95% CI, −9.7 to −3.6). However, only about two-thirds of patients in RCTs responded meaningfully to the procedure with an SBP decrease of 5 mm Hg or more, and reliable predictors of blood pressure response to renal denervation are not currently established.[73,74] After renal denervation, most patients continue to require antihypertensive medications, although often at lower doses or with fewer medications. Long-term follow-up data show sustained blood pressure lowering associated with renal denervation. A meta-analysis of 6 RCTs and 12 observational studies including 2220 patients with hypertension (including resistant hypertension) demonstrated a reduction from baseline in office SBP of −23.0 mm Hg (95% CI, −26.8 to −19.1; 15 studies [2040 participants]) and in 24-hour ambulatory SBP of −13.6 mm Hg (95% CI, −16.5 to −10.8; 11 studies [1018 participants]) after a mean follow-up of 4.4 years (range, 3-9.4).[80] However, RCTs of renal denervation include highly selected patients who were often at relatively low cardiovascular risk and without comorbidities such as stage 4 CKD, and the renal denervation procedures were performed by physicians with specialized training in the procedure.

Procedural vascular complications at the femoral artery access site were reported in 8 of 1598 patients (0.5%) undergoing renal denervation vs 2 of 1197 (0.17%) in the sham-control group (OR, 1.69 [95% CI, 0.57-5.00]).[79] A meta-analysis of 50 studies including randomized and nonrandomized trials and registries (5769 patients) reported an annual incidence of renal artery stent implantation to treat renal artery stenosis as a complication following renal denervation using radiofrequency energy of 0.2% per year (95% CI, 0.12%-0.29%).[81]

The 2025 AHA/ACA guideline recommends that a detailed evaluation should be performed to exclude secondary causes of hypertension prior to renal denervation and that renal denervation should be considered for patients with resistant hypertension whose blood pressure remains elevated despite optimal antihypertensive therapy, including MRA, or for patients who are intolerant of or have contraindications to MRA.[3] In contrast, the European Society of Hypertension guidelines support renal denervation as an option after true resistant hypertension is confirmed.[3,23,24,73,74] The decision to proceed with renal denervation should involve shared decision-making with the patient and treating clinicians, but access may be limited by its cost and need for specialized expertise.

Prognosis

Patients with resistant hypertension have a higher rates of hypertension-mediated organ damage compared with patients with controlled hypertension of similar duration.[82] In a large Spanish observational cohort study in which 8146 patients with controlled hypertension and 8577 with resistant hypertension were followed up until death or for 5 to 10 years, true resistant hypertension confirmed by 24-hour ABPM (≥130/80 mm Hg) was associated with an increased risk of cardiovascular mortality (adjusted HR, 1.68 [95% CI, 1.43-1.98]; absolute risk increase: 10.3% [95% CI, 8.7%-12.1%]) and all-cause mortality (adjusted HR, 1.45 [95% CI, 1.32-1.60]; absolute risk increase, 26.2% [95% CI, 23.5%-28.9%]) over a median follow-up of 9.7 years.[83]

Investigational Therapies

Investigational treatments include selective inhibitors of aldosterone synthesis such as baxdrostat[84] or lorundrostat,[85] which can lower both blood pressure and serum aldosterone in patients with resistant hypertension. In addition, small interfering RNA agents (such as zilebesiran) inhibit the translation of the angiotensinogen messenger RNA, resulting in almost complete suppression of angiotensinogen production by the liver. Angiotensinogen is the precursor to angiotensin I subsequently converted by ACE to angiotensin II, a potent vasoconstrictor.[86] In a phase 2 RCT, 1491 patients with untreated stage 2 hypertension or uncontrolled hypertension despite taking 1 to 2 antihypertensive medications randomly received open-label indapamide, amlodipine, or olmesartan for 4 weeks. Of these, 663 patients with 24-hour ambulatory SBP of 130 mm Hg or greater and less than 160 mm Hg were rerandomized to a single subcutaneous dose of zilebesiran (600 mg) or placebo added to background therapy.[87] At 3 months, compared with placebo + each background therapy (indapamide, amlopidine, or olmesartan), 24-hour ambulatory SBP was reduced by −12.1 mm Hg (95% CI, −16.5 to −7.6)

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with zilebesiran + indapamide, by −9.7 mm Hg (95% CI, −12.9 to −6.6) with zilebesiran + amlodipine, and by −4.5 mm Hg (95% CI, −8.2 to −0.8) with zilebesiran + olmesartan.[87]

Limitations

This review has limitations. First, some relevant publications may have been missed. Second, a formal quality assessment of the included articles was not performed. Third, few RCTs have exclusively enrolled patients with true resistant hypertension. Fourth, many patients with resistant hypertension have comorbidities that may confound outcomes.

Conclusions

True resistant hypertension affects 10% of patients treated for hypertension and is diagnosed after excluding white-coat hypertension by out-of-office blood pressure measurements, medication nonadherence, and secondary hypertension such as primary aldosteronism. First-line treatment includes lifestyle modifications and diuretic therapy with chlorthalidone and combination tablets of antihypertensives. Spironolactone and renal denervation decrease blood pressure in patients with true resistant hypertension.

ARTICLE INFORMATION

Accepted for Publication: January 29, 2026.

Published Online: March 23, 2026. doi:10.1001/jama.2026.1221

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Conflict of Interest Disclosures: Dr Azizi reported receiving grants from Novartis, AstraZeneca, Recor, and Sonivie and receiving personal fees from Novartis, AstraZeneca, Recor, Sonivie, Servier, Alnylam, Boehringer Ingelheim, Novo Nordisk, and Medtronic outside the submitted work. Dr Vongpatanasin reported receiving consulting fees from AstraZeneca both during the conduct of the study and outside the submitted work. Dr Fisher reported receiving grants from Recor Medical and receiving consulting fees from Recor Medical, AstraZeneca, Aktiia, and Alnylam outside the submitted work. Dr Mahfoud reported receiving personal fees from Ablative Solutions, Medtronic, Merck, and Recor during the conduct of the study; receiving grants from AstraZeneca, Inari, Novartis, and Philips outside the submitted work; receiving support from Deutsche Forschungsgemeinschaft (SFB TRR219, Project-ID 322900939) and Deutsche Herzstiftung, paid to a former employer, Saarland University, which has received scientific support from Ablative Solutions, Medtronic, and ReCor Medical; and, until May 2024, receiving speaker honoraria/consulting fees from Ablative Solutions, AstraZeneca, Inari, Medtronic, Merck, Novartis, Philips, and ReCor Medical outside the submitted work. Dr Amar reported receiving lecture fees from AstraZenenca outside the submitted work. Dr Kirtane reported receiving research grants to Columbia University and/or Cardiovascular Research Foundation from Abbott Vascular, Amgen, Biotronik, Boston Scientific, Bolt Medical, CathWorks, Concept Medical, Cordis, Magenta Medical, Medtronic, Neurotronic, Philips, ReCor Medical, and Supira (also includes fees paid to Columbia University and/or Cardiovascular Research Foundation for consulting and/or speaking engagements in which Dr Kirtane controlled the content); holding equity options in Bolt Medical, Airiver, Aeroflow, Lumen Medical, and Tonic Medical; receiving consulting fees from Sonivie; and receiving travel expenses and meals from Amgen, Medtronic, Biotronik, Boston Scientific, Abbott Vascular, CathWorks, Concept Medical, Novartis, Philips, Abiomed, ReCor Medical, Chiesi, Supira, and Shockwave outside the submitted work.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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